142. An animal cell comprising an exogenous isolated polynucleotide of claim 123.

143. A kit for amplifying a portion of a human *FEZ1* gene, the kit comprising an isolated polynucleotide of claim 123 and a second polynucleotide that is homologous with a portion of the opposite strand of SEQ ID NO: 1.

B15 Cont

144. A kit for selecting an anti-cancer therapeutic compound for administration to a human afflicted with a cancer, the kit comprising a plurality of candidate anti-cancer therapeutic compounds and a reagent for assessing expression of *FEZ1* in a cell, wherein the reagent comprises a polynucleotide. --

REMARKS

Claims 23, 24, and 100-144 are pending in this application after entry of this Amendment. Claims 1-22, 25, 27, 30, 34-36, 41-43, 45, 47-58, 63-68, 73-75, 84, 86, 87, and 90-97 have been canceled. New claims 100-144 have been added. Claims 23, 24, 100, 123, and 144 are independent claims. No additional claim fee is believed to be due, since 63 claims (including 7 independent claims) have been canceled and only 45 claims (including 3 independent claims) have been added. No new matter is added by these amendments, as set forth in the following section.

The Applicants note with gratitude that the Examiner has indicated that claims 23 and 24 are in condition for allowance.

Support in the Specification

Support for each of the amendments is found at least in the text of the specification at page 34, page 40, lines 9-12, and page 46, lines 26-28, in the Sequence Listing, and in the claims 1-25, 67, 90, 91, and 94-97, as originally filed.

The specification has been amended to insert sequence identifiers inadvertently omitted upon filing of the application, to conform the figure legends with the newly submitted formal drawings, and to correct other typographical errors. No new matter is inserted by these amendments to the specification. A marked up copy of the amended specification paragraphs, showing the changes made, is enclosed as a separate paper, pursuant to 37 C.F.R. § 1.121.

New formal drawings have been submitted to replace those originally filed with the application. Figure 23 has been amended to correct two minor typographical errors/omissions. A marked up copy of Figure 23, showing the changes made is enclosed with this amendment. Addition of "A_{350}" to the vertical axis of Figure 23 is supported in the specification at page 120, lines 2-12.

The Applicants have not yet received a form PTO-948 Notice of Draftsperson's Patent Drawing Review, and request that the form be completed based on the drawings submitted with this Amendment.

Each of the issues discussed in the Office Action (Paper No. 12) is addressed below in the order it was presented by the Examiner. Unless otherwise indicated, all references to paragraph numbers refer to the numbered paragraphs of Paper No. 12.

I. Election/Restrictions.

The Examiner has acknowledged the Applicants' election with traverse of the claims designated Group I. The Applicants have canceled the remaining claims (claims of Groups II-XXI) without prejudice to the filing of claims encompassing the same subject matter in one or more additional patent applications. Claim 144, a rewritten version of 67, is drawn to a reagent that is a polynucleotide.

II. Sequence Compliance.

At page 3 of Paper No. 12 (paragraphs 5 and 6), the Examiner has asserted that the application fails to comply with 37 C.F.R. § 1.821(a)(1) and (a)(2), because four nucleotide sequences disclosed in this application were not given sequence identifiers.

The specification has been amended to designate these sequences at SEQ ID NOs: 61-64. Paper and computer readable copies of the Sequence Listing, each containing the sequences of SEQ ID NOs: 61-64, are submitted herewith.

III. Priority.

At page 4 of Paper No. 12, the Examiner asserts that claims 91 and 97 are not enabled by the specification of U.S. provisional application 60/121,537, the application to which the present application claims priority, and consequently she has assigned the subject matter of claims 91 and 97 an effective filing date of February 25, 2000. While not agreeing with the Examiner, the presently-pending claims (claims 91 and 97 having been canceled) are distinguishable over all art cited; therefore the Applicants do not comment on the Examiner's statement at this time, although they do reserve the right to do so in a future response, if necessary.

IV. Drawings.

At page 5, paragraph 8, the Examiner has objected to the drawings, specifically to Figure A new Figure 23, containing the correct spelling of "minutes" and the addition of "A_{350}" as a Y-axis label, is submitted in clean form. Thus, the Examiner's objection is no longer applicable, and its withdrawal is respectfully requested.

V. Objections to the Specification.

At page 5, paragraph 9 of Paper No. 12, the Examiner has objected to the specification because of the absence of Figure 5. Figure 5, which was inadvertently omitted from the application upon filing, is submitted herewith. The inclusion of Figure 5 does not constitute new matter as a substantially identical "Figure 5" (i.e., identical except for the format of the numbering of the Figures) is present in the U.S. provisional application from which this application claims priority, U.S. provisional application serial no. 60/121,537, filed February 25, 1999.

The Examiner has objected to the specification on the basis of several typographical errors. First, the Examiner asserts that, at page 17, line 17 of the specification, the sequence of Figure 4B is incorrectly identified. The Applicants have amended the specification to correct this typographical error.

The Examiner asserts that the protein "KIAA0522" is inconsistently labeled in the specification and in the Sequence Listing. The Applicants are unable to find a place in the sequence listing where the term "KIAA0522" is used. It is requested that the Examiner withdraw this objection, or else provide to the Applicants more information describing the problem in a subsequent communication, so they may better address it.

The Examiner has asserted that Figure 9 appears to be the results of the experiment presented at page 107, lines 11-19. Figure 9 does indeed show the results of that experiment, and the relevant portion of the specification has been amended to indicate this.

Additionally, the specification has been amended in several places to remedy minor typographical errors.

In light of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw her objections to the specification.

VI. Objections to the Claims.

At page 6, paragraph number 10 of Paper No. 12, the Examiner has objected to claim 19 for use of the language "polynucleotides are linked by non-naturally occurring linkage other than a phosphodiester linkage." The Examiner requests correction of the claim, contending that "a phosphodiester linkage is not a non-natural linkage in polynucleotides." Claim 19 has been canceled. None of the new claims contains the language to which the Examiner has objected. Thus, this objection is now inapplicable.

The Examiner informs the Applicants that, should claim 4 be allowed, she will object to claim 94 as being substantially duplicative. Claims 4 and 94 have been canceled. Therefore, it is submitted that the objection is no longer applicable.

In light of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw her objections to the claims.

VII. Rejections Under 35 U.S.C. § 112, first paragraph.

At pages 6-9 of Paper No. 12, the Examiner has rejected claim 67, asserting that it is not enabled by the description provided in the specification. In particular, the Examiner argues that, based upon the broad scope of the claims, the unpredictability and complexity of cancers, the lack of sufficient guidance or working examples in the specification, and the quantity of experimentation necessary, it would require undue experimentation by one of skill in the art to determine how to use the claimed kit for selecting an anti-cancer therapeutic compound for administration to a human afflicted with cancer. The Applicants have canceled claim 67; however, they respectfully traverse the rejection should it be applied to any of the new claims, for the reasons given below.

To be fully enabling, the specification must teach a person of ordinary skill in the art how to make and use the claimed invention without undue experimentation. M.P.E.P. § 2164.01. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* The absence of a working example does not necessarily establish that a claim is not enabled. M.P.E.P. § 2164.02.

The specification of this application, read in light of the level of skill of an ordinarily skilled artisan, is fully enabling of the full scope of the subject matter of claim 67. The claim is directed to a kit for selecting an anti-cancer therapeutic compound. The kit comprises candidate anti-cancer therapeutic compounds and a polynucleotide reagent for assessing expression of *FEZ1* in a cell.

A person skilled in the art would be fully taught how to make and use the invention upon review of the specification and in view of the knowledge a skilled artisan in this area would have. The specification discloses that various tumors, such as prostate tumors, breast tumors, head and neck squamous cell carcinomas, urinary bladder carcinomas, hepatocellular carcinomas, and hematological malignancies are associated with allelic losses on chromosome 8p. *See, e.g.,* page 2, lines 4-15. At page 82, the specification teaches how to make the claimed kit, *see,* page 82 at lines 1-9, and the sequences for the various polynucleotides which could be used as reagents for use in the kit Are provided throughout the specification, as are suggested

methods for making and/or isolating such polynucleotides. Candidate anti-cancer compounds for use in the kit are also described in the specification, and are well known in the art. *See,* page 30, at lines 1-5. As the Examiner herself recognizes, the level of one of skill in this art is high; thus, in view of the high level of skill and the teachings provided in the specification, the subject matter of claim 67 is fully enabled.

Finally, the Applicants respectfully point out, that contrary to the Examiner's assertion, it is not necessary that a skilled person understand how a given candidate anti-cancer therapeutic compound (identified using a kit such as that recited in claim 67) affects expression of *FEZ1*, in order to practice the invention, but only that she understand how such candidate anti-cancer compound may affect the cancer for which the assessment of expression of *FEZ1* in a cell provides information. *See,* specification at page 30, lines 1-5, (describing the various anti-cancer therapeutic compounds which may be used in the practice of the invention). Anti-cancer compounds and their efficacy in various types of cancers are well known in the art, and are effectuated through various physiological or intracellular mechanisms. A skilled person in the art is well aware that the selection of a particular anti-cancer therapeutic compound varies widely; such determinations are based upon many factors, including the type of cancer, the stage to which the cancer has progressed, and the genetic composition, the physiology and/or the medical history of the particular patient. Given these complexities, a skilled person routinely engages in at least some degree of experimentation to determine or select a proper anti-cancer therapeutic compound.

Accordingly, the full scope of claim 67 is enabled by the specification as filed. It is respectfully requested that the Examiner reconsider and withdraw her rejection under 35 U.S.C. § 112, first paragraph, and not apply the rejection to the new claims.

VIII. Rejections Under 35 U.S.C. § 112, second paragraph.

At page 10 of Paper No. 12, the Examiner has rejected claims 2, 7, 14, 16, 20-22, 25, 91, 95, and 97 under 35 U.S.C. § 112, first paragraph as being indefinite for various reasons. First, the Examiner argues that use of the term "has" or "having" renders each of the claims

unclear, as it is "unclear" whether such terms are open or closed. The Applicants traverse this rejection for the reasons set forth below.

The phrase "having the sequence" is not indefinite, as a nucleic acid has (and can only have) but one sequence. Thus, a nucleic acid that "has" a sequence can have only that sequence. Of course, a class of nucleic acids can be described as "having" a sequence that comprises a sub-sequence, meaning that the sequence of every nucleic acid in the class includes at least the sub-sequence and can include other sequences. Thus, "having" used to describe the sequence of a nucleic acid is a closed term, while "comprising" is an open term. The Applicants remind the Examiner that a sequence is a property of a chemical compound, just as molecular weight and chemical structure are properties. A molecule "has" only one value for each of these properties at any given time.

At paragraph 15, the Examiner has rejected claim 16 as being "unclear" because immobilization is purported not to be "a detectable label." Claim 16 has been canceled; however the Applicants would traverse this rejection if it were to be applied to any of the new claims. Claim 16 recites "a detectably labeled isolated polynucleotide" (not "a detectable label" as the Examiner suggests). Reading the specification, it is clear that "an immobilized polynucleotide" is a "detectably labeled isolated polynucleotide," as it permits the detection of a desired polynucleotide or protein and is understood to a person of ordinary skill in the art to be encompass a protein or polynucleotide within the definition of "detectably labeled" provided in the specification at, for example, page 29, lines 1-7. *See,* page 29, lines 5-6 (stating that methods of detectably labeling a protein or polynucleotide include "surfaces with which such compounds are linked.")

The Examiner also rejected claim 18 as indefinite for use of the term "substantially purified," asserting that such term renders the claim "vague and indefinite." Claim 18 has been canceled; however the Applicants would traverse this rejection if it were to be applied to any of the new claims. Use of the term "substantially" does not render a claim indefinite, as long as one of ordinary skill in the art would understand what is claimed, in light of the specification. M.P.E.P. § 2173.05(b). In the present case, the term "substantially purified" is defined specifically at page 23, lines 9-12 of the specification. For example, according to the

specification, a person of ordinary skill would recognize that "a substantially purified polynucleotide is one which is separate from at least most of the components that naturally accompany it in its naturally occurring state, and preferably from at least 75%, 80%, 90% or even 95% of those components, as assessed on a per-weight basis or a per-mole basis." Accordingly, as the term "substantially purified" is defined with precision and clarity in the specification, the Applicants submit that use of such term does not render the claim indefinite.

Also at page 10, the Examiner has rejected claim 20 for use of the term "in combinations of such linkages." Claim 20 has been canceled; none of the new claims contains this language.

The Examiner rejected claim 21 as well, asserting that the phrase "an end of the isolated polynucleotide is nucleolytically blocked" is vague and indefinite. Claim 21 has been canceled; however, the Applicants would traverse this rejection if it were to be applied to any of the new claims. The phrase is neither vague nor indefinite when read in light of the specification, specifically, page 38, lines 14-18. This portion of the specification describes how the stability of the isolated polynucleotides can be enhanced by blocking the ends of the polynucleotide from attack by nucleases. The specification refers to an art reference which itself provides the details related to the use of such agents to enhance the stability of isolated nucleic acids. *See,* page 38, lines 16-18. Thus, a person of ordinary skill could easily ascertain the meaning of "nucleolytically blocked;" its use does not render the claim vague or indefinite.

Finally, the Examiner rejected claim 97 for use of the phrase "the portion is substantially with at least fifty consecutive nucleotide residues." Claim 97 has been canceled; thus, the rejection is no longer applicable.

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw her 35 U.S.C. § 112, second paragraph, rejections, and not apply the rejections to the new claims.

IX. Rejections Under 35 U.S.C. § 102.

The Examiner has rejected claims 1-5, 8-16, 18, 22, and 90-97 under various subparts of 35 U.S.C. § 102, based upon one or more of the following references, each taken individually:

(i) European Patent No. 0679716 A1 of Matsubara *et al.* ("Matsubara");

(ii) U.S. Patent No. 5,804,177 of Humphries ("Humphries");

(iii) U.S. Patent No. 5,840,686 of Chader *et al.* ("Chader");

(iv) Wang *et al.* (1998) Science 280: 1077-1082 ("Wang");

(v) Database EST, Accession No. N21184 ("the N21184 reference");

(vi) Database EST, Accession No. AI04290 ("the AI04290 reference"); and

(vii) Ishii *et al.* (1999) Proc. Natl. Acad. Sci. U.S.A. 96: 3928-3922 ("Ishii").

The Applicants traverse these rejections for the reasons given below.

First, as a threshold matter, the Applicants respectfully point out that the Ishii reference is not properly cited as prior art to this application under any subpart of 35 U.S.C. § 102. Ishii describes the inventor's own work. Each of the claims was invented by one or more of Carlo M. Croce or Hadeshi Ishii, the named inventors of the invention, and the authors of Ishii. The other authors of the Ishii reference were merely co-authors and did not invent the subject matter of the pending claims. Accompanying this response is a Declaration of Carlos Croce which establishes those facts. This Declaration is presently unexecuted; an executed version will be supplied shortly. Consequently, the Ishii reference is not properly cited as prior art. It is requested that the Examiner reconsider and withdraw any rejections based upon Ishii.

Second, with regard to the remaining six references, the Applicants submit that none teaches each element of the invention, as presently claimed, and therefore none anticipates it. Matsubara teaches only a sequence of nucleotide residues homologous with residues 8454 to 8844 of SEQ ID NO: 1.

Humphries teaches a sequence that is homologous with at least twenty consecutive nucleotide residues of each nucleotide residues 4420 to 4450, residues 4344 to 4364, and residues 6918 to 6938 of SEQ ID NO: 1.

Wang teaches a sequence having a homology with at least twenty consecutive nucleotide residues of each nucleotide residues 7634 to 7740 and residues 7742 to 7805 of SEQ ID NO: 1.

The N21184 reference teaches a sequence homologous with at least twenty consecutive nucleotide residues of SEQ ID NO: 1 at residues 8521 to 8559, at residues 8586 to 8616, at residues 8679 to 8823, at residues 8826 to 8898, or at residues 8963 to 9042.

Finally, the AI04290 reference teaches a sequence homologous with at least twenty nucleotide residues of nucleotide residues 424 to 870 of SEQ ID NO: 1.

In contrast the claimed invention is, *inter alia*:

(i) an isolated polynucleotide of at least twenty nucleotide resides of specific portions of SEQ ID NO: 1 (portions at residues 1 to 423, residues 871 to 4343, residues at 4365 to 4419, residues 4451 to 4473, residues 4514 to 6917, 6939 to 7633, and residues 7806 to 8520);

(ii) an isolated polynucleotide that is substantially homologous to at least twenty nucleotide residues of one of the portions of SEQ ID NO: 1 listed above;

(iii) a pharmaceutical composition comprising one of these isolated polynucleotides;

(iv) an animal cell containing one of these isolated polynucleotides; and

(v) several kits containing the isolated polynucleotides.

None of the references discloses the isolated polynucleotides, the kits, or the animal cells of the invention. Accordingly, none of the six references cited by the Examiner anticipates the claimed invention. Nor does Ishii anticipate the claimed invention, as it is not properly cited as prior art.

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw all of the § 102 rejections asserted at pages 11 to 13 of Paper No. 12, and not apply the rejections to the new claims.

X. Rejection Under 35 U.S.C. § 103

At pages 13 to 15 of Paper No. 12, the Examiner is has rejected claims 1-5, 14, 17, and 94-97 as being unpatentable (obvious) in view of the N21184 reference, taken in view of Lockhart *et al.* (1996) Nature Biotech., 14: 1675-1680 ("Lockhart"). The Examiner asserts that the N21184 reference discloses the claimed polynucleotides and that Lockhart discloses gene chips containing high density oligonucleotide arrays for use with sequences from the human genome. Claims 1-5, 14, 17, and 94-97 have been canceled, but the Applicants traverse the rejection, should it be applied to the new claims.

The teachings of N21184 reference are discussed above, in part IX of this response. Lockhart discloses polynucleotides arrays included in gene chips.

To establish a *prima facie* case of obviousness under 25 U.S.C. § 103, the Examiner has the burden of demonstrating: (i) that the proposed combination teaches or suggests each element of the claimed invention; (ii) that a person of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner, based upon the teachings of the references; and (iii) that a person of ordinary skill would have had a reasonable expectation that such combination would be successful. In the present situation, the Examiner has failed to meet the burden.

First, the N21184-Lockhart combination as suggested by the Examiner ("the combination") neither teaches nor suggests each element of the claimed invention. As discussed above, the N21184 reference does not disclose the claimed polynucleotide of the invention, nor does it disclose the kits, animal cells, or pharmaceutical compositions containing the polynucleotide of the invention. Lockhart, which is applied solely for its teaching of polynucleotide-containing gene chips, does not remedy the deficiencies of N21184, because it also does not disclose the claimed polynucleotide. Consequently, the combination suggested the Examiner neither teaches nor suggests each element of the invention and therefore it does not render it obvious.

Second, as the polynucleotide sequences of the claimed invention were unknown before their disclosure by the Applicants, a person of ordinary skill would not have found it obvious to make the combination suggested by the Examiner, nor would she have had a

reasonable expectation that making the combination would give rise to the polynucleotide, animals cells, pharmaceutical compositions, or kits of the present invention.

Accordingly, in light of the foregoing, reconsideration and withdrawal of the Examiner's § 103 rejection is respectfully requested.

CONCLUSION

In view of the above, it is respectfully submitted that pending claims 23, 24, and 100-144 are fully compliant with all requirements of 35 U.S.C. § 101 *et seq.* and are distinguished over all cited art. Accordingly, reconsideration and allowance of claims 23, 24, and 100-144 are earnestly solicited.

For the Examiner's convenience, a clean copy of all pending claims, in an appropriate order, is appended to this response.

Respectfully submitted,

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24 Oct 2001
(Date)

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Enclosures: Petition for Extension of Time
Marked –Up Version of Amended Specification Paragraphs
Marked Up Version of Figure 23
Transmittal of Formal Drawings
Replacement Formal Drawings (80 sheets)
Substitute Sequence Listing: paper and electronic copies + Statement to Support
Declaration of Carlo M. Croce
Clean Copy of All Pending Claims

MARKED UP VERSION OF AMENDED SPECIFICATION PARAGRAPHS

U.S. Patent Application No. 09/513,988 of Croce et al.

In accordance with 37 C.F.R. § 1.121, below are marked up version of the paragraphs of the specification, showing the changes made by the amendments submitted in the made by the response filed August 27, 2001, in the above-identified patent application.

As used herein, added text is underlined and deleted text is ~~struck-through~~.

Page 13, paragraph at lines 16 to 25:

Figure 1A, comprising Figures 1Ai-1Aviii, is a series of representative LOH analysis results obtained using tissue samples obtained from two patients, designated E26 and E46. Figures 1Ai, 1Aiii, 1Av, and 1Avii depict results from tissue obtained from patient E26. Figures 1Aii, 1Aiv, 1Avi, and 1Aviii depict results from tissue obtained from patient E46. In each figure, fluorescent PCR products were generated by amplification of DNA obtained from normal (N) and tumor (T) tissue samples from the corresponding patient, and products were separated by size. For each tracing, the horizontal axis represents DNA fragment size, and the vertical axis (i.e. peak height) represents relative amount of each fragment. Figures 1Ai and 1Aii correspond to D8S264; Figures 1Aiii and 1Aiv correspond to LPL; Figures 1Av and 1Avi correspond to D8S136; and Figures 1Avii and 1Aviii correspond to FGFR1. Several fragment sizes (in base pairs) are indicated.

Paragraph at page 13, lines 26, to page 14, line 5:

Figure 1B is a diagram which depicts a summary of LOH analyses described herein. Results for each patient who exhibited LOH at least at one locus are shown. Filled circles represent loss of an allele. Circles containing a cross represent non-informative results owing to homozygosity at the corresponding locus. Open circles represent retention of both alleles. ~~Dark shaded~~ Cross-hatched areas of the diagram represent regions of allele loss. ~~Light shaded~~ Hatched areas represent regions of non-informative results within the allele-loss area. The numbers atop each column refer to individual patients. The designations beside each row

refer to polymorphic markers. The region near the marker *D8S261* locus, described herein, is boxed.

Page 17, paragraph at lines 17 to 29:

Figure 2 comprises Figures 2A, 2B, 2C, and 2D. The predicted Fez1 amino acid sequence (SEQ ID NO: 4) is depicted in Figure 2A. Figure 2A lists the predicted amino acid sequence of FEZ1 protein, as derived from the *FEZ1* cDNA. Underlined amino acid residues represent a region homologous to the DNA-binding domain of ATF-5 protein. Double-underlined amino acid residues represent a leucine zipper motif, in which repeated leucine residues are ~~shaded~~ indicated. Heavily-underlined amino acid residues are residues which can be phosphorylated by either a cAMP/cGMP-dependent kinase (serine residue 29) or a tyrosine kinase-dependent kinase (tyrosine residue 67). Dashed-underlined regions represent regions having related amino acid sequence motifs. Serine and threonine residues in bold or thin dotted lines represent potential casein kinase II and protein kinase C, respectively, phosphorylation sites. -Triangles indicate exon boundaries. Asterisks represent missense or nonsense mutation sites.

Page 15, paragraph at lines 1 to 7:

In Figure 2B, the predicted amino acid sequence of a region (amino acid residues 301-369; SEQ ID NO: 6) of Fez1 corresponding to the predicted DNA binding and leucine zipper regions is compared with the analogous regions (SEQ ID NOs: 7 and 8, respectively) of proteins Atf-5 and KIAA0522. Identical amino acid residues are indicated by ~~dark shading~~ double underlining, and similar amino acid residues are indicated by ~~light shading~~ single underlining. Gaps introduced by the FASTA program are represented by "-". Closed circles are used to indicate repeated leucine residues.

Page 17, paragraph at lines 6 to 16:

Figure 4 comprises Figures 4A and 4B. Figure 4A is a diagram which depicts truncated *FEZ1* transcripts observed in cancer cells, as described herein. The normal exon/intron

structure is indicated on the top line of the diagram, and was determined by sequencing of normal (i.e. non-cancerous) brain, prostate and esophagus cDNAs and by sequencing *FEZ1* gene in BAC. Boxes represent exons; the ~~shaded~~ hatched areas represent the open reading frame (1788 base pairs; SEQ ID NO: 3). Horizontal lines represent introns, and closed circles represent point mutations which were observed, as described herein. The boxed notation "LZ" represents the approximate location of the leucine-zipper motif described herein. "FS" represents the approximate position of a frame-shift described herein. Aberrant transcripts observed in tumors are depicted by bold lines on the lines below the top line in the diagram.

Page 17, paragraph at lines 17 to 20:

Figure 4B is the putative amino acid sequence (SEQ ID NO: ~~6)~~ 5) encoded by the frame-shifted *FEZ1* transcript having a molecular weight of about 8.6 kilodaltons. Amino acid residues encoded by the frame-shifted portion of the transcript are underlined.

Paragraph at page 13, lines 26, to page 14, line 5:

Figure 5, comprising Figures ~~5A-5P~~ 5A-1 to 5Q, is a series of nucleotide and amino acid sequences. Figure 5A comprises Figures ~~5Ai-5Aiv~~ 5A-1 to 5A-6, and lists the nucleotide sequence (SEQ ID NO: 1) of a portion of the human genome comprising the *FEZ1* gene. Figure 5B comprises Figures ~~5Bi-5Biii~~ 5B-1 to 5B-4, and lists the nucleotide sequence (SEQ ID NO: 2) of a cDNA which reflects the nucleotide sequence of the full-length mRNA transcript of wild type *FEZ1*. Figure 5C lists the nucleotide sequence (SEQ ID NO: 9) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (E16T8) *FEZ1* mRNA transcribed by tumors cells. Figure 5D lists the nucleotide sequence (SEQ ID NO: 10) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (E264162) *FEZ1* mRNA transcribed by tumors cells. Figure 5E comprises Figures ~~5Ei~~ 5E-1 and ~~5Eii~~ 5E-2, and lists the nucleotide sequence (SEQ ID NO: 11) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (T8D145M4) *FEZ1* mRNA transcribed by tumors cells. Figure 5F comprises Figures 5F-1 and 5F-2 and lists the nucleotide sequence (SEQ ID NO: 12) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated

(D14) *FEZ1* mRNA transcribed by tumors cells. Figure 5G comprises Figure 5G-1 and 5G-2 and lists the nucleotide sequence (SEQ ID NO: 13) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (G3611) *FEZ1* mRNA transcribed by tumors cells. Figure 5H comprises Figures ~~5Hi~~ 5H-1 and ~~5Hii~~ 5H-2, and lists the nucleotide sequence (SEQ ID NO: 14) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (G3612) *FEZ1* mRNA transcribed by tumors cells. Figure 5I comprises Figures 5I-1 and 5I-2 and lists the nucleotide sequence (SEQ ID NO: 3) of a cDNA which reflects the nucleotide sequence of the ORF region of wild type *FEZ1* mRNA. Figure 5J comprises Figures 5J-1 to 5J-5 and lists the amino acid sequence (SEQ ID NO: 4) of full-length, human wild type Fez1 protein. Figure 5K lists the amino acid sequence (SEQ ID NO: 15) of a truncated (E16T8) Fez1 protein expressed by tumors cells. Figure 5L comprises Figures 5L-1 and 5L-2 and lists the amino acid sequence (SEQ ID NO: 16) of a truncated (E264162) Fez1 protein expressed by tumors cells. Figure 5M comprises Figures 5M-1 to 5M-4 and lists the amino acid sequence (SEQ ID NO: 17) of a truncated (T8D145M4) Fez1 protein expressed by tumors cells. Figure 5N comprises Figures 5N-1 to 5N-4 and lists the amino acid sequence (SEQ ID NO: 18) of a truncated (D14) Fez1 protein expressed by tumors cells. Figure 5O comprises Figures 5O-1 to 5O-5 and lists the amino acid sequence (SEQ ID NO: 19) of a truncated (G3611) Fez1 protein expressed by tumors cells. Figure 5P comprises Figures 5P-1 to 5P-5 and lists the amino acid sequence (SEQ ID NO: 20) of a truncated (G3612) Fez1 protein expressed by tumors cells. Figure 5Q lists the nucleotide sequence (SEQ ID NO: 21) of the *F37* probe described herein.

Page 19, paragraph at lines 1 to 4:

Figure 7, comprising Figures 7A (clone 15), 7B (clone 54), 7C (clone 18), and 7D (clone 118), is a quartet of graphs which indicate the time dependence of the ratio of transfected MCF7 clone cell number to control cell number for cells maintained in tetracycline-free medium containing 10% (○), 5% (●), 2.5% (□), 1% (■), or 0.5% (▲) (v/v) fetal bovine serum.

Page 20, paragraph at lines 1 to 4:

Figure 14, comprising Figures 14A, 14B, 14C, and 14D, is a series of four images which depict the results of immunoblotting experiments involving HeLaS3 cells which were co-transfected with a vector encoding a V5/Fez1 fusion protein and a vector encoding an EXP/EF1-γ fusion protein.

Page 26, paragraph at lines 16 to 21:

By describing two polynucleotides as "operably linked", it is meant that a single-stranded or double-stranded nucleic acid moiety comprises the two polynucleotides arranged within the nucleic acid moiety in such a manner that at least one of the two polynucleotides is able to exert a physiological effect by which it is characterized upon the other. By way of example, a promoter operably linked with the coding region of a gene is able to promote transcription of the coding region.

Page 29, paragraph at lines 10 to 16:

A "gene chip" is a manufacture comprising a surface having an ordered array of polynucleotides attached thereto, either permanently or reversibly. For example, the ordered array may comprise four sections, wherein one of four polynucleotides is attached to the surface in each section, and wherein the four polynucleotides have nucleotides sequences which are identical with the exception of one nucleotide residue (e.g. 5'-AACCAAAAAAA-3' (SEQ ID NO. 61); 5'-AACCAAAAAAT-3' (SEQ ID NO. 62); 5'-AACCAAAAAAC-3' (SEQ ID NO. 63); and 5'-AACCAAAAAAG-3' (SEQ ID NO. 64).

Page 56, paragraph at lines 10 to 24:

The invention includes a method of determining the cancerous status of a sample tissue. This method comprises comparing *FEZ1* expression in the sample tissue with *FEZ1* expression in a control tissue of the same type. Decreased *FEZ1* expression in the sample tissue, relative to *FEZ1* expression in the control tissue, is an indication that the sample tissue is cancerous. The sample tissue can be a phenotypically abnormal tissue (e.g. a biopsy sample

obtained from a potentially cancerous lesion in a human tissue such as breast or prostate), or it can be a phenotypically normal tissue. The control tissue is a non-cancerous tissue of the same type, and can be obtained from the same human from whom the sample tissue was obtained, or from one or more humans different than the one from whom the sample tissue was obtained. If a body of data ~~exist~~ exists or ~~are~~ is created, from which a representative value for expression of *FEZ1* in non-cancerous tissue of the same type as the sample tissue, then *FEZ1* expression in the sample tissue can be compared with this representative value, rather than performing a separate determination of *FEZ1* expression in the same or a different human.

Page 106, paragraph at lines 10 to 24:

The effect of *FEZ1* expression *in vitro* cell growth of MCF7 cells was analyzed using the CellTiter 96™ Aqueous non-radioactive cell proliferation assay obtained from Promega Corporation (Madison, WI) per the supplier's instructions. The absorbance of the MTS compound of the assay system at 490 nanometers exhibited a linear correlation between the number of MCF7 cells in a range between 102 and 104 cells, as confirmed by cell counting in which dead cells were excluded ~~the dead cells~~ by tryptan blue staining. Cells of clones 15, 18, 54, and 118 were selected in wells of 96-well plates containing tetracycline-free medium supplemented with 10, 5, 2.5, 1, or 0.5% (v/v) FBS. Culture medium was exchanged daily with the corresponding fresh medium. Absorption at 490 nanometers was assessed in order to estimate the number of cells present in each well at selected times. The results of these experiments are presented in Figure 7, in which data are shown as a ration of the number of transfected cells to the number of control mock MCF7 transfectants (i.e. transfected with vector alone) cultured in the corresponding medium. Data were calculated as an average of four independent experiments, and bars in Figure 7 indicate the standard deviations.

Page 107, paragraph at lines 11 to 19:

About 5×10^6 or about 2×10^7 cells (MCF7 cells transfected with the pTet-Off™ vector alone o rMCF7 transfectant clone 15, 18, 56, or 118 clone cells) were subcutaneously inoculated into the left dorsal subclavicular region of 6 week-old female

Balb/nude mice. Four mice were used for each experimental group. Tumor volume was estimated for each mouse by measuring in two directions using Vernier calipers, and was calculated as tumor volume=length × $(\text{width})^2/2$. These results indicate that expression of *FEZ1* inhibited proliferation of MCF7 cells *in vivo*, and indicate that *FEZ1* expression inhibits (or even reverses) proliferation of epithelial tumor cells in animals. The results of these experiments are presented in Figure 9.